Myosin Modulator (Mavacamten): A Novel Oral Treatment for Obstructive HCM

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Disclosure: Consultant MyoKardia
Drug Therapy in HCM

1. Beta-Blockers (Braunwald) ....... 1964

2. Verapamil (Kaltenbach) ............ 1979

3. Disopyramide (Pollick) ............. 1982

No New Drug Therapy for HCM for 35 Years
Recent Investigational Pharmacologic Trials in HCM:

- Angiotensin II Inhibitors
- Aldosterone Inhibitors
- Late Na Channel Inhibitors
- Metabolic Modulator

• Myosin Modulator
Oral Myosin Modulator (Mavacamten)

“Precision Medicine”

• Drug Binds to the “off-actin” state of Myosin... *interrupts Myofilaments*

• Decrease power Stroke of contraction

Mavacamten: Decreases Systolic Function (Lowes EF)

“Negative Inotrope”

Potential Treatment for Obstructive HCM
Mavacamten Initiative:

1. Phase I (Safety and Tolerability)
2. PIONEER- HCM (Phase II)
3. Explorer-HCM (Phase III)
Mavacamten Initiative:

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PIONEER-HCM (Open Label)

- n = 11 → n = 10 (one SAE)
- 56 years old (22-70 years)
- NYHA class II (n=7); NYHA Class III (n=4)
- Rest EF = 70 ± 7%
- Rest LVOT Gradient = 68 ± 34 mmHg
- Mavacamten 10 or 15 mg for 12 weeks (Off BB or CCB)
- Primary End-point = Gradient Reduction
Concordant Change in Resting LVOT Gradient and EF (n=10)

Significant Proportion of HCM Patients:

- EF ≤42% (One SD)
- EF ≤29% (Two SD)

“Powerful Drug”
Change in NYHA Functional Class (n=10)

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>Baseline</th>
<th>12 Week</th>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>7</td>
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<tr>
<td>2</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
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</tbody>
</table>

3 out of 10 (30%) No Improvement in Symptoms

Heitner S et al HFSA 2017
### PIONEER-HCM: Safety

#### Non-Serious AE

<table>
<thead>
<tr>
<th></th>
<th># of events</th>
<th># assessed related to study drug</th>
<th># of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>LVEF Reduction</td>
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<td>3</td>
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<tr>
<td>Atrial Fibrillation</td>
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<td>1</td>
<td>2</td>
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<tr>
<td>Dizziness</td>
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<td>0</td>
<td>1</td>
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<tr>
<td>Dyspnea Exertional</td>
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<td>1</td>
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</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
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#### Serious AE

One Patient Recurrent AF (2x) requiring DCCV and Antiarrhythmic Tx

Patient Elected to **Stop** Mavacamten at Week 4

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Change in Peak VO$_2$ at 12 Weeks

Baseline: 20 ml/kg/min
12 Weeks: 24 ml/kg/min

$p = 0.004$

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Mavacamten Initiative:

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3. Explorer-HCM (Phase III)
Explorer-HCM

n = ~200-250 obstructive HCM pts
Primary End-Point = peak VO$_2$
Relation Between Ejection Fraction (Contractility) and Gradient Reduction in HCM

- Disopyramide: $\Delta EF = \downarrow 5-10\%$
- Mavacamten: $\Delta EF = \downarrow$
- Myectomy: $\Delta EF = \text{None}$

$\Delta EF = \text{Benefit } \sim 60\%$

$\Delta EF = \geq 15\%$

$\Delta EF = \text{Benefit } \sim 95\%$
You Can Obliterate Gradients with a Drug, But at What Cost?...
Average Duration of Time on Drug (If approved): ~>30 years

Long-term Effects of Manipulating Structural Apparatus of the HCM Heart?

Duration of Time on Drug (Phase III): ~6-12 months
Potential Impact of Mavacamten on EF in US HCM Population (If approved)

~150,000 HCM Patients in U.S.

~100,000 Obstructive HCM Pts.

~20,000 HCM Pts on Mavacamten with EF<42%
(Avg. age of 45 years)
Mavacamten in Obstructive HCM

• Novel oral myosin inhibitor showing promising *early* data demonstrating efficacy at lowering outflow tract gradients and potentially improving functional capacity

• Awaiting completion of larger randomized studies to inform short term efficacy and both short and longer term safety
HYPERTROPHIC CARDIOMYOPATHY
A Contemporary and Treatable Genetic Disease: Diagnosis, Heart Failure Management, and Prevention of Sudden Death